

PATENT IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:

LIM *et al.*

APPLICATION No.: 10/623,481

FILED: 18 July 2003

FOR: **DUAL DRUG DOSAGE FORMS WITH
IMPROVED SEPARATION OF DRUGS**

EXAMINER: YOUNG, Micah-Paul

ART UNIT: 1618

CONF. No: 4558

APPELLANT'S BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
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Sir:

The present paper is Appellants' Appeal Brief submitted in compliance with 37 C.F.R. § 41.37(c), and is an appeal to the Board of Appeals and Interferences from the decision of Examiner Young in the Final Office action mailed February 19, 2010 (hereinafter "Final Office Action"), to maintain the rejection of claims 1-18.

REAL PARTY IN INTEREST

The real party in interest is Depomed, Inc., the assignee of record of all right, title and interest in the present application.

RELATED APPEALS AND INTERFERENCES

No other prior or pending appeals, interferences or judicial proceedings are known to Appellants, the Appellants' legal representative, or Assignee, which may be related to, directly affect, or be directly affected by or have a bearing on, the Board's decision in the pending appeal.

STATUS OF CLAIMS

Claims 1-18 are pending and are the subject of this appeal. These claims are presented in APPENDIX A.

STATUS OF AMENDMENTS

Appellant's amendment after final, dated May 24, 2010, was entered and made of record.

SUMMARY OF CLAIMED SUBJECT MATTER

The sole independent claim is directed to a method for the manufacture of a pharmaceutical tablet. The claimed method manufactures a tablet having a first drug in an immediate release outer layer separated from a second drug in an inner core by a drug-free polymer layer that dissolves upon ingestion of the tablet (§ [0004]). The method of manufacture comprises the steps of:

- (a) dispersing the second drug in a solid matrix to form a unitary body which upon immersion in gastrointestinal fluid releases the second drug by prolonged release (§ [0006]);
- (b) depositing on a surface of the unitary body a polymeric film that is devoid of either the first drug or the second drug (§§ [0004], [0015]), the polymeric film formed from a polymer (i) effective to prevent interaction of the second drug and the first drug prior to administration of the dosage form and (ii) which dissolves in gastrointestinal fluid upon ingestion (§ [0015]);
- (c) depositing over the polymeric film a fluid medium comprising the first drug and a liquid carrier that does not remove the polymeric film upon contact therewith (§§ [0014], [0018]); and
- (d) evaporating the liquid carrier from the fluid medium thus deposited to leave a solid layer containing the first drug over the unitary body (original claim 1, part (d)).

GROUND OF REJECTION TO BE REVIEWED ON APPEAL

The issue for review on appeal is whether claims 1-18 are obvious under 35 U.S.C. §103 over Johnson *et al.*, U.S. Patent No. 6,171,618 (hereinafter "Johnson").

ARGUMENT

The rejection of the pending claims as allegedly obviousness over Johnson is grounded on both legal and factual errors, which are addressed below. First, however, a summary of Johnson is provided followed by a synopsis of each party's position.

A1. SUMMARY OF JOHNSON

JOHNSON discloses dosage forms designed for the immediate release of cetirizine and the sustained release of pseudoephedrine (Abstract; Col. 1, lines 56-64). Johnson describes two alternative dosage forms (Col. 3, lines 17-27; Col. 4, lines 51-63) to achieve the immediate release and sustained release of these drugs. The first dosage form design is described on Col. 2, lines 1-9:

"...this invention provides a solid dosage form comprising cetirizine and pseudoephedrine, wherein at least a portion of said pseudoephedrine is contained in a core comprising said portion of pseudoephedrine, said core being surrounded by a permeable membrane, whereby release of said pseudoephedrine into an environment of use is sustained...:

Thus, the first dosage form has a pseudoephedrine drug core surrounded by a permeable membrane that controls release of drug from the core. An immediate release layer of the second drug cetirizine is coated on the permeable membrane (Col. 2, lines 8-9; Col. 2, lines 37-40). The drug core in this embodiment is an *immediate release* drug core, as evident from at these passages:

"...the pseudoephedrine core can comprise a shaped pseudoephedrine immediate release composition and a surrounding, rate limiting membrane which imparts sustained release behavior to the core" (Col. 3, lines 23-27);

".....the pseudoephedrine core can be formed from an immediate release, pseudoephedrine-containing composition which is surrounded by a water insoluble, permeable, rate-limiting membrane that provides for sustained release of pseudoephedrine by limiting the rate at which pseudophedrine diffuses into the environment of use." (Col. 4, lines 52-58).

The second dosage form disclosed in Johnson is comprised of a pseudoephedrine sustained release core coated with a polymer/cetirizine immediate release layer, as described in these passages:

"This invention further provides a process for making a solid dosage form containing cetirizine and pseudoephedrine, comprising coating a shaped sustained release core comprising pseudoephedrine with an immediate release layer comprising cetirizine and a water soluble film forming polymer..." (Col. 2, lines 22-27)

"The sustained release pseudoephedrine is contained in a core which can be engineered in a variety of ways and embodiments to implement sustained release. For example, the pseudoephedrine can be incorporated into a sustained release matrix that meters pseudoephedrine out over a period of 4 to 36 hours..." (Col. 3, lines 17-22)

Thus, the second dosage form design has a sustained release drug core surrounded by an immediate release layer of cetirizine.

These two alternative dosage form embodiments are also clearly and unequivocally set forth in at least these passages of Johnson:

Col. 3, lines 17-27: For example, the pseudoephedrine can be incorporated into a sustained release matrix that meters pseudoephedrine out over a period of 4 to 36 hours, the matrix thus constituting the core. Alternatively, the pseudoephedrine core can comprise a shaped pseudoephedrine immediate release composition and a surrounding, rate limiting membrane which imparts sustained release behavior to the core.

Col. 4, lines 51-61: As previously mentioned the core can be a matrix which meters out pseudoephedrine. Alternatively, the pseudoephedrine core can be formed from an immediate release, pseudoephedrine-containing composition which is surrounded by a water insoluble, permeable, rate-limiting membrane that provides for sustained release of pseudoephedrine by limiting the rate at which pseudoephedrine diffuses into the environment of use. The core is in turn

coated over at least a portion of its surface with a layer comprising cetirizine and a water soluble film forming polymer that provides immediate release.

A2. SUMMARY OF EXAMINER'S POSITION

The Examiner has maintained the rejection in reliance on four assertions:

(i) Johnson teaches a controlled release core surrounded by a drug-free matrix then further coated with a drug layer, as recited in the instant claims (Final Office Action, page 3, point 5);

(ii) The subject matter of the instant claims differs from that of Johnson only in disclosure of the ratio of unitary dosage form to polymeric film (Final Office Action, page 3, point 4);

(iii) While the instant claims require that the drug-free membrane dissolves, the claims don't recite how much dissolution must occur and thus read on the membrane pores disclosed in Johnson, which are formed when portions of the modulating membrane dissolve (Final Office Action, page 6, last paragraph); and

(iv) Appellants "speculate" that the polymers recited in the instant claims and the polymers of Johnson have different characteristics but provide no data to this effect, and that the speculated elements are not present in the instant claims (Final Office Action, page 5).

A3. SUMMARY OF APPELLANT'S POSITION

No *prima facie* case of obviousness has been established because Johnson fails to show or suggest each and every element of the claimed method.

The pending method claims recite steps for the manufacture of a dosage form comprising three layers: (a) a second drug in a solid matrix core which provides prolonged release of the second drug, (b) an intermediate polymeric film, deposited on the matrix core, that is devoid of first or second drug, formed from a polymer effective to prevent interaction between first and second drugs and which dissolves upon ingestion, and (c) a first drug in a fluid medium that is deposited onto the intermediate polymeric film and which evaporates to form a solid layer containing the first drug.

Johnson nowhere shows or suggests a method for manufacture of tablet having this structure. Of the two dosage forms described in Johnson, only one involves a drug core surrounded by drug-free polymer layer. However, this dosage form in Johnson is comprised

of an *immediate release core* surrounded by a rate-limiting polymer membrane. Because it is the rate-limiting polymer membrane that provides the sustained release from the drug core, it is evident that the rate-limiting polymer membrane *does not dissolve upon ingestion* (if it did dissolve, there would be no sustained release from the immediate release core). Moreover, this dosage form in Johnson has an *immediate release core*, in contrast to a solid matrix core which provides *prolonged release* of drug in accord with the presently claimed method.

The Examiner's continued rejection of the claims is grounded in two errors: (1) mischaracterizing, misinterpreting or failing to understand both Appellants' disclosure and the disclosure in Johnson, and (2) failing to consider all of the elements recited in the pending claims. With respect to the first error, the Examiner has failed to comprehend that Johnson discloses two alternative dosage forms, and improperly combines passages from the separate and distinct embodiments in Johnson in a failed attempt to arrive at a dosage form in accord with the claimed method of manufacture. With regard to the second error, the Examiner is of the mind that the present claims do not specify that the solid matrix containing the second drug provides sustained release, despite claim 1(b) expressly stating that the solid matrix forms a unitary body "which upon immersion in gastrointestinal fluid releases said second drug by prolonged release". Since the rejection is grounded in error, Appellants urge its reversal.

B. Analysis

The legal and factual errors in the rejection are addressed individually below.

B1. LEGAL ERROR: NO PRIMA FACIE CASE OF OBVIOUSNESS HAS BEEN ESTABLISHED BECAUSE JOHNSON FAILS TO SHOW OR SUGGEST ALL OF THE ELEMENTS OF THE INSTANT CLAIMS

To establish a *prima facie* case of obviousness, three basic criteria must be met. The third criterion is that the prior art references (or references when combined) must teach or suggest all the claim limitations.

The claimed method comprises, *inter alia*, depositing on a surface of the unitary body formed by dispersing the second drug in a solid matrix, a polymeric film that is devoid of either the first or second drug, and which dissolves in gastrointestinal fluid upon ingestion.

Johnson discloses two embodiments of a dosage form for immediate release of cetirizine and sustained release of pseudoephedrine. With reference to section A1 above, in one embodiment, the dosage form has an immediate release pseudoephedrine core

surrounded by a rate-limiting polymer membrane which is coated with an immediate release layer of cetirizine. In the second embodiment, the dosage form has a pseudoephedrine sustained release core coated with a polymer/cetirizine immediate release layer.

The second embodiment clearly lacks the element in the instant claims of an intermediate polymeric film disposed between the pseudoephedrine sustained release core and the polymer/cetirizine immediate release layer. Therefore, any method of manufacture of the dosage form in the second embodiment of Johnson cannot involve each and every step in the claimed method.

With regard to the dosage form in the first embodiment of Johnson, the sustained release of pseudoephedrine is achieved by the rate-limiting polymer membrane that surrounds the immediate release pseudoephedrine core. The rate-limiting polymer membrane is detailed in Johnson at Col. 5, lines 9-32, where it is described that the membrane is permeable by means of, for example, a pore size in the membrane that allows passage of water and dissolved pseudoephedrine, or permeable only to water and comprising a hole or opening for release of pseudoephedrine (*see also*, Col. 7, line 49 to Col. 9, line 55).

The dosage form in this second embodiment of Johnson provides sustained release of pseudoephedrine for 4-36 hours (Col. 5, line 20), and therefore the rate-limiting polymer membrane must remain capable of its rate-limiting function for at least 4 hours. The polymer membrane, therefore, cannot dissolve in gastrointestinal fluid upon ingestion.

Moreover, the dosage form in the second embodiment of Johnson has an *immediate release* pseudoephedrine core. In contrast, the dosage form manufactured in accord with the claimed method has as its core a "unitary body which upon immersion in gastrointestinal fluid releases the second drug by prolonged release". The core of the dosage form in Johnson if placed in gastrointestinal fluid would immediately release the drug, and is incapable of providing a prolonged release.

Accordingly, Johnson fails to show or suggest a dosage form that has a prolonged release core surrounded by a polymeric film that dissolves upon ingestion which is coated with an immediate release layer, and therefore cannot be said to show or suggest a method of manufacturing such a dosage form. A *prima facie* case of obviousness is, therefore, not established.

B2. TECHNICAL ERROR: THE EXAMINER FAILS TO COMPREHEND THAT JOHNSON DESCRIBES
TWO SEPARATE DOSAGE FORM EMBODIMENTS

The Examiner's failure to grasp that Johnson discloses separate and alternative embodiments of dosage forms to provide sustained release of pseudoephedrine is causative in the rejection, and glaringly apparent in the Office actions, as evidenced in the following statement by the Examiner:

"The first drug (the controlled release agent) is released so that at least 75% of the drug is released over a period of 4-36 hours (col. 3, lin. 10-15). The first drug is formed into a core with a solid matrix material such as microcrystalline cellulose and hydroxypropyl cellulose (col. 17, lin. 50-55)....
...The resultant coated core is further coated with a drug formulation (col. 18, lin. 30-40). The tablets are dried leaving a solid two drug controlled release agent with the top drug formulation releases immediately while the inner coated drug releases slower (examples)." (Final Office Action, page 3, point 5).

At Col. 3, lines 10-15, Johnson refers to the sustained release of the first drug (pseudoephedrine) by either 1) an immediate release drug core surrounded by a drug-free rate-limiting membrane, or 2) a sustained release drug core. The passage at Col. 17, lines 50-55 in Johnson list the formulation for an immediate release drug core only. In this passage from the Final Office action set forth above, the Examiner implies that the core of microcrystalline cellulose and hydroxypropyl cellulose is a sustained release core, when in fact it is not. The Examiner omits the fact that a core of microcrystalline cellulose and hydroxypropyl cellulose is an immediate release component that requires a semi-permeable membrane to achieve sustained release.

Moreover, the Examiner then states in point 5 on page 4 of the Final Office action that:

"The core is then coated with a solution of a polymer matrix not comprising a drug..."

In fact, the sustained release core of Johnson is not coated with a drug-free polymer matrix.

Clearly, the Examiner does not understand the distinctions between the two dosage forms of Johnson or that Johnson describes two different dosage form embodiments. Rather, the Examiner "mixes and matches" the teachings of Johnson at Col. 3 and Col. 17 to allege that Johnson teaches a dosage form comprising a *sustained release* drug core coated

by a drug free layer. In fact, to assert that Johnson teaches or suggests a sustained release core surrounded by a drug-free intermediate layer is simply and completely incorrect.

B3. TECHNICAL ERROR: THE EXAMINER FAILS TO UNDERSTAND THE STRUCTURAL FEATURES OF
THE DOSAGE FORMS DESCRIBED IN JOHNSON

The Examiner asserts that because Johnson discloses that portions of the rate-limiting membrane can dissolve upon exposure to gastrointestinal fluid (Johnson, Col. 10, lines 35-50), and since Johnson and the instant claims recite polyvinyl alcohol as a materials for the polymeric film, the rate-limiting polymer in Johnson must be equivalent to the claimed feature of a polymeric film that is devoid of either the first or second drug, and which dissolves in gastrointestinal fluid upon ingestion (Final Office action, page 5, second full paragraph, *"Since the polyvinyl alcohol of the instant claims results in a membrane being dissolved in the gastrointestinal tract it follows that the polyvinyl alcohol membrane of the '618 patent would dissolve as well."*) This is technically incorrect.

Polymers such as those taught by the present specification and by the cited reference, are well known in the art for the diverse structural and functional properties they may impart on the compositions that contain them. Such properties are routinely modified through variation of, for example, the amounts and molecular weights of a given polymer present in the composition. One of skill in the art would know under what conditions (i.e., amounts, molecular weight, presence of other components), a particular polymer would, for example, form a water-insoluble membrane or form a membrane which dissolves immediately upon exposure to fluid. Polyvinyl alcohol, is taught in Johnson at Col. 9, lines 9-25, as a polymer to be used in making a rate-limiting membrane which surrounds an immediate release composition. One of skill in the art, when making a rate limiting membrane, would incorporate a polyvinyl alcohol polymer of an appropriate molecular weight, degree of cross-linking, etc. in order to provide a membrane that does not dissolve upon exposure to gastrointestinal fluid so as to function as a rate-limiting membrane for 4-36 hours. In contrast, polyvinyl alcohol used to form the dissolvable film of the instant claims would be of a molecular weight, degree of cross-linking, etc. to provide a film that dissolves upon exposure to gastrointestinal fluid.

Accordingly, Appellants submit that the polymeric film which dissolves in gastrointestinal fluid upon ingestion, is not taught or suggested by Johnson and therefore a *prima facie* case of obviousness has not been established.

The Examiner also asserts that Appellants "speculate" that the polymers recited in the instant claims and the polymers of Johnson have different characteristics but provide no data to this effect, and that the speculated elements are not present in the instant claims (Final Office Action, page 5). Specifically, the Examiner agrees that

"molecular weight, cross-linking, etc., can change a polymer's properties, yet none of these properties [sic] have been claimed or recited anywhere in the instant claims or specification."

This position is wrong. One of skill in the art would know under what conditions (i.e., amounts, molecular weight, presence of other components) a particular polymer would, for example, form a water-insoluble membrane or form a membrane which dissolves immediately upon exposure to fluid. By functionally specifying that a polymer film is formed of a polymer that dissolves in gastrointestinal fluid upon ingestion, and that prevents interaction of the first and second drugs prior to ingestion, the properties of the polymer are set forth. Obviously, polymers that do not dissolve or that are permeable to the first or second drug do not satisfy the requirements of claim 1(b). In this way, Appellants have defined the properties of the polymers, and it is therefore incorrect to state that Appellants argue elements not present in the claims.

Moreover, the Examiner supports his position with a wholly incorrect interpretation of the technical aspects of Johnson. The Examiner states that with respect to the dosage form in Johnson:

"The drug-free membrane surrounding the sustained release second drug unitary body comprises leachable materials such as polyvinyl alcohol and semi-permeable materials such as cellulose acetates. These components would form a film that dissolves in gastrointestinal fluid." (Final Office action, page 6, lines 2-5).

To support this position, the Examiner references passages in Johnson at Col. 8, lines 50-55 and Col. 9, line 25 to Col. 10, line 55.

The Examiner has completely failed to understand that these sections of Johnson describe two vastly different membrane layers that may be applied to the immediate release drug core matrix. Notably, polyvinyl alcohol is listed as a water insoluble polymer which is used in forming an impermeable membrane, through which, for example, a passageway may be produced to allow drug release (Col. 8, lines 29-30). Moreover, cellulose acetate is also water insoluble. The combination of polyvinyl alcohol and cellulose acetate will not, does not, and cannot form a "film that dissolves in gastrointestinal fluid", as the Examiner asserts.

Nor is the Examiner's position supported by Johnson's disclosure of a porous membrane that encases the immediate release drug core, in which the pores form after exposure to fluid as the water soluble additives are leached out of the membrane (Col. 10, lines 35 - Col. 11, line 49). Membrane-forming polymers comprising pore-formers are described at least in Col. 10, lines 35-54 of Johnson. Polyvinyl alcohol is not listed as a pore former.

Appellants submit that the Examiner is again mixing up the various embodiments of Johnson. The Examiner is picking and choosing from unrelated embodiments in Johnson in an unsuccessful attempt to piece together the claimed method. With all due respect, the Examiner's utter failure to technically understand the teaching of two dosage forms in Johnson illustrates a complete failure to bear in mind the recitations in claim 1 and has lead to faulty reasoning in maintaining the obviousness rejection. Claim 1 requires a polymer film that dissolves in gastrointestinal fluid, and, there is nothing in the disclosure of Johnson that shows or suggests a dosage form having a drug-free polymeric film that dissolves upon ingestion in gastrointestinal fluid.

Accordingly, for all the reasons set forth above, the obviousness rejection of claims 1-18 is in error and should be reversed. Appellants respectfully request the Board to do so.

Respectfully submitted,

Date: 17 December 2010

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APPENDIX A

1. (Previously presented) A method for the manufacture of a pharmaceutical tablet which upon oral ingestion delivers a first drug by immediate release and a second drug by prolonged release defined as a release rate into gastrointestinal fluid that is slow enough to leave at least about 40% of said second drug unreleased one hour after ingestion, said method comprising:

- (a) dispersing said second drug in a solid matrix to form a unitary body which upon immersion in gastrointestinal fluid releases said second drug by prolonged release;
- (b) depositing on a surface of said unitary body a polymeric film that is devoid of either said first drug or said second drug, said polymeric film formed from a polymer (i) effective to prevent interaction of the second drug and the first drug prior to administration of the dosage form and (ii) which dissolves in gastrointestinal fluid upon ingestion;
- (c) depositing over said polymeric film a fluid medium comprising said first drug and a liquid carrier that does not remove said polymeric film upon contact therewith; and
- (d) evaporating said liquid carrier from said fluid medium thus deposited to leave a solid layer containing said first drug over said unitary body.

2. (Previously presented) The method of claim 1 in which said solid matrix is comprised of a member selected from the group consisting of celluloses, substituted celluloses, microcrystalline cellulose, polysaccharides, substituted polysaccharides, poly(alkylene oxide)s, poly(vinyl alcohol), starch, starch-based polymers, crosslinked poly(acrylic acid)s, and substituted crosslinked poly(acrylic acid)s.

3. (Previously presented) The method of claim 1 in which said solid matrix is comprised of a member selected from the group consisting of poly(ethylene oxide), hydroxypropyl methyl cellulose, and combinations of poly(ethylene oxide) and hydroxypropyl methyl cellulose.

4. (Previously presented) The method of claim 1 in which said polymeric film is comprised of a member selected from the group consisting of poly(ethylene oxide), hydroxypropyl methyl cellulose, polyvinyl alcohol, combinations of poly(ethylene oxide) and

hydroxypropyl methyl cellulose, and combinations of polyvinyl alcohol and poly(ethylene oxide).

5. (Original) The method of claim 1 in which said fluid medium comprises a liquid solution of said first drug in a solvent.

6. (Original) The method of claim 1 in which said fluid medium comprises a liquid solution of said first drug and a polymer in a solvent.

7. (Original) The method of claim 1 in which said fluid medium comprises a suspension of said first drug in solid particle form in a liquid suspending agent.

8. (Original) The method of claim 1 in which said fluid medium comprises a suspension of said first drug in solid particle form and a dispersing agent, also in solid particle form, in a liquid suspending agent, said dispersing agent being a substance that separates into discrete particles upon contact with gastrointestinal fluid.

9. (Original) The method of claim 1 in which said fluid medium is an aqueous suspension of said first drug, and said first drug is comprised of particles having a weight-averaged diameter equal to or less than 25 microns.

10. (Original) The method of claim 1 in which said fluid medium is an aqueous suspension of said first drug, and said first drug is comprised of particles having a weight-averaged diameter equal to or less than 10 microns.

11. (Original) The method of claim 1 in which the weight ratio of said polymeric film to said unitary body is from about 0.005:1 to about 0.2:1.

12. (Original) The method of claim 1 in which the weight ratio of said polymeric film to said unitary body is from about 0.01:1 to about 0.1:1.

13. (Original) The method of claim 1 in which the weight ratio of said polymeric film to said unitary body is from about 0.01:1 to about 0.08:1.

14. (Original) The method of claim 1 in which (b) comprises surrounding said unitary

body entirely with said polymeric film, and said solid layer of (d) is a shell completely encasing said unitary body and polymeric film.

15. (Original) The method of claim 1 in which (b) and (c) comprise depositing said polymeric film and said first drug over only a portion of the entire surface of said unitary body, leaving the remainder of said unitary body exposed.

16. (Original) The method of claim 1 in which said liquid carrier of step (c) is water.

17. (Original) The method of claim 1 in which said liquid carrier of step (c) is an organic solvent.

18. (Previously presented) The method of claim 17 in which said organic solvent is comprised of a member selected from the group consisting of ethanol, hexanes, chloroform, carbon tetrachloride, and dimethyl sulfoxide.

EVIDENCE APPENDIX

None

RELATED PROCEEDINGS APPENDIX

None